per c.mm.; colour index, 0.9; white cells, 900 per c.mm. (lymphocytes 80% and neutrophil polymorphs 20%, approximately). No red cell abnormalities were noted. On June 3 the bleeding time was longer than 10 minutes, the clotting time (venous blood) 11 minutes, the prothrombin time 11 seconds (normal, 8 seconds); blood platelets, 3,400 per c.mm.; reticulocytes were not found. The blood was Group O (IV) Rhesus-positive.

Table showing Results of Sternal Punctures

Date	June 3, 1947	Aug. 16, 1947	May 21, 1948
Total nucleated count	3,400 per c.mm.	10,200 per c.mm.	25,000 per c.mm.
Myeloblasts	—	0·4%	1·2%
Premyelocytes	1 seen in 3 films	0·6%	0·8%
Neut. myelocytes	" "	6·8%	9·2%
Neut. metamyelocytes	—	3·4%	8·6%
Neutrophils, segmented	Present	15·0%	24·2%
Eosin. myelocytes	—	1·4%	0·2%
Eosinophils	—	1·0%	0·6%
Basophil myelocytes	—	—	—
Basophils	—	—	0·2%
Lymphocytes	Present	32·0%	29·0%
Monocytes	"	3·2%	2·0%
Megakaryocytes	—	0·2%	Present—mature forms found
Haemocytoblasts	—	1·4%	0·2%
Normoblasts, basophil	1 seen in 3 films	6·8%	2·6%
Normoblasts, polychromatic	—	21·0%	19·8%
Normoblasts, orthochromic	—	6·2%	1·0%
Myeloid: erythroblast ratio	—	1 : 1·6	1·87 : 1
Miscellaneous cells	—	0·4%	0·4%
Naked eye	A fatty fluid	A fatty fluid	Marrow particles very evident

The sternal puncture findings are presented in the accompanying Table. They show a progressive return of cellularity from a condition of almost complete aplasia.

Haematological Progress.—The neutropenia persisted until May 18, 1948, when for the first time the neutrophil polymorphs amounted to more than 2,000 per c.mm. Reticulocytes were not found in any numbers until Feb. 2, 1948, when they totalled 5% of 3,800,000 red blood cells per c.mm. (190,000 per c.mm.). The platelet count did not rise to normal figures until after Feb. 24, 1948, when it was 40,000 per c.mm. On May 21, 1948, the platelet count was normal.

Discussion

It is of interest to note that the last cell series to recover completely in the circulating blood was that of the neutrophil polymorphonuclears. Neutropenia persisted from April, 1947, to May, 1948—a period of 13 months. Reticulocytes did not appear until after nine months of treatment, and platelets returned to normal only after a full 12 months. The capillary resistance test remained positive for seven months. It was felt that, of all the therapeutic agents given, penicillin and blood transfusions were the most important. The former totalled some 35 mega units, administered over a four-months period. The condition of the mouth and legs gave cause for anxiety in the early months, but about the end of the sixth month of the disease a gradual improvement became apparent.

Summary

A case of aplastic anaemia following neoarsphenamine administration is described. Depression was present in all marrow elements—a condition of almost complete aplasia. Recovery was complete after 13 months.

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The Ministry of Health states that hospitals may provide clothing for those "up" patients unable to provide it themselves and who are not obtaining it from other sources such as voluntary organizations. They would normally be long-stay ambulant patients. The patients may retain this clothing after discharge from hospital if the hospital is satisfied that the patients need clothing and are unable to obtain it from their own resources and without help.

HISTAMINE HEADACHE*

BY

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Headache is the most frequent complaint encountered in medical practice. It presents no diagnostic problem: the diagnosis is made by the sufferer. But the doctor must know the cause if he is to treat the patient efficiently.

Table I classifies the forms of headache that I have treated. The present paper is concerned mainly with the type of headache due to histamine, as described by Horton in 1941.

TABLE I.—*Results of Treatment by Histamine*

	Histamine Headache	Migraine	Psychical Headache	"Relaxation" Headache	Alcoholic Headache	Headache Associated with Hypertension	Headache with Organic Basis	Total	Controls without Headache
Complete cure	29	2	2	2	1	2	2	40	Slight or no reaction
Considerable improvement	8	1	2	1	1	1	2	16	
Some improvement	6	2	2	0	0	0	1	11	
No change	2	3	2	0	1	0	5	13	
Total	45	8	8	3	3	3	10	80	10

Clinical Features and Aetiology

Vallery-Radot in 1925, Brickner-Riley in 1935, and Money in 1939 described cases of atypical migraine which seem to be similar to the histamine headache described by Horton. It was Horton, however, who first described the syndrome, made the aetiology clear, produced the same symptoms experimentally, and outlined the method of treatment.

The characteristic symptoms of histamine headache, the frequency of which is shown in Table II, are as follows: it occurs in paroxysms, is unilateral, and is confined to a circumscribed area; on the same side there is congestion of the nasal mucous membrane; attacks frequently come on at night, and the patient often rises in the morning with headache. It is neither hereditary nor familial, has no connexion with menstruation or ocular disturbances, and is unassociated with vomiting. The condition is resistant to all treatment. In these patients headache produced by the injection of histamine is of the same type as occurs spontaneously.

As to the aetiology, it must be presumed that the accumulation of histamine produces an upset in cell metabolism. This accumulation is the result either of overproduction of histamine or of the inhibition of the destructive factor. It is also possible that individual hypersensitivity plays a part in cases in which the production of histamine is normal. According to Horton, in histamine headache the symptoms are caused by dilatation and constriction of the external and common carotid arteries. On the other hand, Wolff, Schumacher, Clark, Butler, Shuterland, and Pickering have proved, on the evidence of many cases, that the internal carotid is responsible for the quality and the intensity of histamine headache, and that the dilatation of the external carotid is of decisive importance in migraine. They demonstrated with photographs, taken during headache produced by the injection of histamine: (1) the amplitude of intracranial pulsation (which is increased); (2) the

*A paper read at the International Congress of Medicine held at Budapest in September, 1948.

TABLE II.—*Typical Symptoms of Histamine Headache*

	Histamine Headache	Migraine	Psychical Headache	"Relaxation" Headache	Alcoholic Headache	Headache Associated with Hypertension	Headache with Organic Basis	Total	Controls without Headache
No of cases	45	8	8	3	3	3	10	80	10
Age	16–60	24–36	20–32	28–59	36–41	49–57	24–37		
Duration	2 months–30 yrs	2–10 years	1 month–1 year	1–6 years	1–2 years	1–2 years	3 months–1 year		
Unilateral	26	5	2	1	1	1	3		
Localized	11	3	6	2	2	2	3		
Generalized	8						4		
Temporal	8	5	2	1		1	2		
Frontal	12	3		2	1		4		
Parietal	14								
Occipital	7								
Vertebral	4								
Paroxsymal	19	8					2		
Nocturnal	16								
Diurnal	29								
Stationary	10		8	3	2	2			
Watering of eyes	12								
Congestion of nasal mucous membrane	16								
Vomiting	2	5			2				

arterial blood pressure ; (3) the pressure of the cerebrospinal fluid ; and (4) the degree of pulsation in the temporal artery.

Increase in the intracranial pressure reduces the pain in histamine headache by providing counter-pressure to the dilated arteries, signifying that the dilatation of these arteries plays a part in the production of this type of headache. In migraine, however, this procedure has no influence on the headache, a fact which implies that dilatation of the extracerebral arteries is the basis of the condition.

Horton noted that repeated administration of the same dose of histamine could produce a progressively diminishing headache ; that is to say, the tolerance of the patient for histamine had increased. These observations led him to try desensitization. The term "desensitization" is used here in its widest sense. The desensitization is non-specific, because specific hypersensitivity is not the aetiological factor and there are symptoms of neither hypersensitivity nor of allergy. But the favourable effect of a long course of small doses demonstrates that the therapeutic effect is in the nature of a desensitization.

It is accepted that, although differing greatly from adrenaline and the choline derivatives in nature and origin, histamine will probably take its place with them among the most important hormones in animal life. Dale and de Krogh have explained the role of histamine in capillary vasodilatation and the regulation of blood pressure. Later, in 1947, Emmelin and Feldberg observed that histamine was a physiological antagonist of adrenaline. So far as we know, histamine is a breakdown product of tissue proteins, which produce an acid of which histamine (β-iminazolylethylamine) is the amine. The release of this amine occurs in shock due to anaphylaxis, trauma, and other causes. The liberation of histamine may be local.

An interesting question confronts us: Why should a symmetrical system respond with pain which is asymmetrical, unilateral, and localized ? It must be presumed that some unknown mechanism makes this possible. The resistance of the arteries to histamine may become less in a circumscribed region and the dilatant effect produced at this point, or some arterial lesion in this area may bring about a local liberation of histamine.

Treatment

In the neurological department of the Szent István Hospital, under Professor Lehoczky, I have treated 90 patients with histamine. They had headache of long duration—between two months and 30 years—which was resistant to all treatment and made them incapable of any work. I have followed up the cases for six months, either by personal contact or by correspondence.

I first gave each patient a test dose of 0.3 mg. of histamine subcutaneously. The local reaction appeared in the form of a red urticarial weal with a surrounding areola of vasodilatation. After several seconds flushing of the face, neck, and chest, and tachycardia occurred ; a few minutes later a localized headache began in the usual site. This reaction could be reproduced exactly in all cases of histamine headache. In atypical cases a stronger dose of histamine was necessary to produce the same reaction. In ten control cases not suffering from headache the injection caused a feeble reaction or no response at all, in two cases resulting in only a mild headache, which disappeared in a few minutes.

The symptoms generally continued for from ten minutes to three or four hours. The next day I began desensitization with an injection of 0.1 mg of histamine subcutaneously, and continued the treatment on the following day according to the reaction to the preceding dose. If the headache, tachycardia, and rise in blood pressure were too severe I reduced the dose. Tolerance increased after the first three or four injections, and I therefore progressively increased the daily dose to 0.2 mg. There are recorded in the literature intradermal and intravenous treatments with various solutions of histamine in extremely high dosage for periods of two to three months, but with my method I obtained the same results in less time (Table I).

Case Reports

The following cases illustrate the course of treatment.

Case 1.—A woman aged 48, suffering from headache for thirty years, which was always confined to the frontal region on the right side. She had had several courses of treatment without result. After *x*-ray examination the headache was attributed to osteitis of the frontal bone. The patient came to me in a state of depression and was unable to work because of the very severe headache. After the first four injections the headache ceased. She received ten further injections. Five months after the treatment was finished the headache had not returned.

Case 2.—A woman of 24, suffering for six years from headache which was becoming more and more severe. It was always situated in the right temporal region and on the crown. She had to get up five or six times during the night because of the headache. The attacks often occurred during the daytime, and were accompanied by nasal obstruction and watering of the eyes. At the site of the subcutaneous injection there was a local reaction. One or two minutes afterwards she experienced a headache corresponding exactly to her spontaneous attacks. After ten injections she could leave hospital. She has since informed me that she no longer suffers from headache.

Case 3.—A woman aged 49 had had headache since the birth of her son, who is now 28. This was not precisely the type of headache associated with histamine. The pain was stationary and made her incapable of work. She tried several treatments in vain and was driven to ideas of suicide. After the first five

injections she had no more headache. She received one injection a day during the next two weeks, and her previous complaints—loss of appetite, depression, fatigue, and vertigo—all disappeared. She now does hard work on the land in extreme heat. She receives one injection a week and is free of symptoms.

Case 4.—A man aged 59 suffered for six years from headache in the frontal and occipital regions. The attacks began when he had finished his hard mental work and left for his week-end rest. This is headache of the "relaxation" type, such as is experienced by a priest on a Monday and by students after an examination. Haemoconcentration reduces the volume of blood, and the relaxed arterial walls are not able to resist the dilatant effect of histamine. After seven injections the patient was free of symptoms for six weeks. He was taking small doses of ergotamine tartrate during this period. The headaches then recurred, but twenty further injections completely cured him.

Comment

I have never observed any severe side-effects. The injection of histamine influences the blood pressure and the pulse for only a few minutes. I have therefore used this therapy in heart disease, hypertension, and hypotension. Palpitations occurred in the first days of treatment, but diminished during the course of desensitization. Several patients experienced a metallic or acid taste in the mouth shortly after injection, one patient had diarrhoea which lasted a week, and vomiting occurred after the first two injections administered to a patient with hyperchlorhydria. But, despite these disagreeable secondary effects, I have on more than one occasion heard the patient say, "I am a new man."

The important point of this therapy is that the patient is completely relieved of his pain at the end of treatment and requires no other remedies. I have reached the conclusion that treatment by histamine is worth while in all cases of frequent headaches of long duration.

Summary

The clinical features and possible pathogenesis of headache due to histamine are discussed. A course of treatment by injections of histamine is described. Details are given of four patients so treated.

Medical Memoranda

Unusual Case of Coronary Thrombosis

There is both clinical and pathological evidence that thrombosis occurs at the site of a previous sclerotic or atheromatous area in a coronary vessel. The event that initiates the thrombosis is, however, very variable, and in many instances may not be apparent. The following case is interesting in view of the dramatic nature of the immediate cause of the infarction.

Case Report

A man aged 49 was seen at Professor Robert Platt's outpatient clinic and gave the following history. He had known for some years that he was abnormally sensitive to a wasp-sting, as he had previously developed severe generalized angioneurotic oedema immediately following a sting. Some months ago he had again been stung on the ankle and within ten minutes felt extremely ill, vomited, and had a sudden attack of diarrhoea. He perspired profusely and had agonizing precordial pain, as though there were a tight band around the chest. Simultaneously he developed severe angioneurotic oedema of the face and had a rigor. The next day the symptoms had subsided except for the precordial pain, which lasted for a further two days before disappearing; there was some fever at this time and he complained of shortness of breath. Seven weeks later he had no complaints except slight residual dyspnoea. Physical examination revealed no abnormalities; the blood pressure was within normal limits.

A clinical diagnosis of myocardial infarction was made. This was confirmed by electrocardiography, which showed sharp inversion of the T waves in the limb Lead I and in the unipolar precordial Leads V4 and V6, the changes being typical of anterior myocardial infarction.

Comment

This would seem to be a case of coronary thrombosis which was precipitated by a severe immediate allergic reaction following a wasp-sting. Numerous cases have been reported previously in which thrombosis followed conditions causing shock and sudden fall of blood pressure. Boas (1942), in a review of immediate causes of cardiac infarction, mentions non-penetrating chest injuries, effort, emotion, allergy, cold, infectious disease, operation, and haemorrhage. Among cases classed as due to allergy, one occurred during serum sickness a week after an injection of tetanus antitoxin; one occurred six hours after an intravenous injection of typhoid vaccine; and another developed symptoms of coronary insufficiency after prophylactic pollen injections for hay-fever. Lockhart (1939) reports another case of coronary thrombosis, proved at necropsy, which occurred three hours after an intravenous injection of typhoid vaccine, death taking place one hour later.

Although no records are available of blood-pressure readings during the acute phase of the illness, it is well known that a severe anaphylactic reaction may cause a sudden fall in arterial blood pressure. Such a fall in blood pressure may have precipitated infarction in the case reported.

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A Case of Curling's Ulcer

In 1842 Thomas Curling described an acute ulcer in the second part of the duodenum as a complication of extensive cutaneous burns or scalds. He stated that the ulcer was situated opposite the ampulla of Vater, and described it as small, clean-cut, and deep. Following this description cases of this condition were reported from many places in Britain, on the Continent, and in America. It was suggested that toxins were excreted in the bile, apparently on the supposition that the bile is secreted with such force as to impinge on the opposite wall of the duodenum and ignoring the fact that it is secreted only when food is in the duodenum. A more reasonable hypothesis is an infected embolus from the burnt area, though why infarction should always occur in the same area is not explained.

More recently cases have only rarely been reported. Some textbooks continue to give an adequate description of the condition, others make no mention of it, while some cast a varying degree of doubt over its very existence. Ross (1925), for example, states that "its occurrence is practically unknown and grave doubt has been cast on the statement" (of the occurrence of this complication of burns). The following case is reported to show that such an ulcer does occur, and that it is a complication of burns. It may be objected that the scalds were neither very extensive nor very severe, but an ulcer due to any other cause at the age of 6 years and in the second part of the duodenum is more improbable.

Case Report

On Aug. 26, 1947, a Chinese boy aged 6 years was admitted to the District Hospital, Ipoh, with second-degree scalds from hot water on the lower part of the back of the trunk, the